# 高敏感方法检测肌钙蛋白（hs-cTnI）、心型脂肪酸结合蛋白（H-FABP）临床应用

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# 门、急诊胸痛中心快速诊断ACS方法学进展



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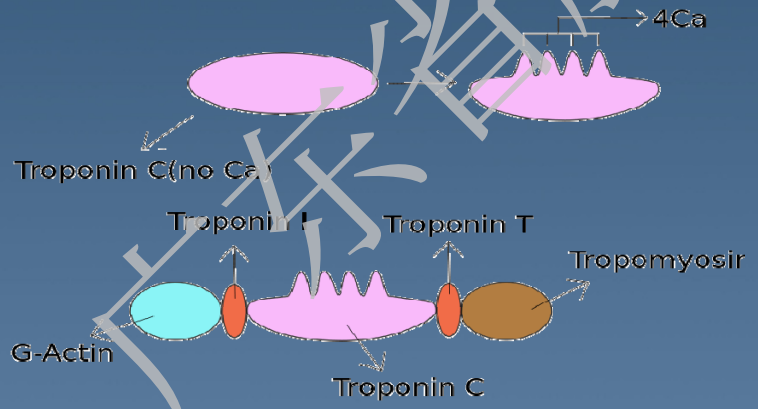
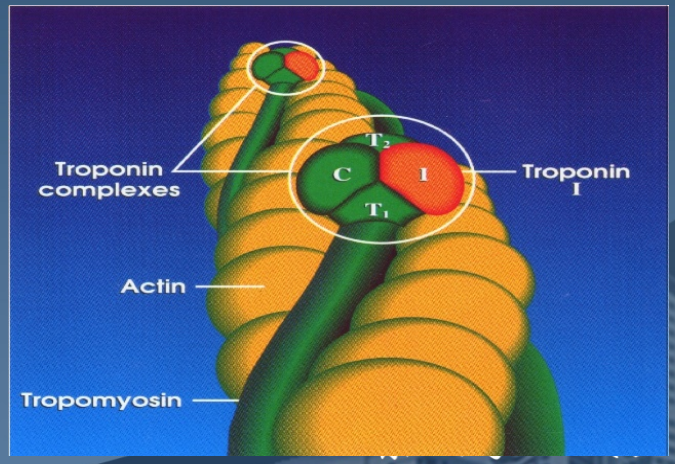
# hs-cTnI的检测

20 世纪 90 年代后期，传统的 cTnI 和 cTnT 检测系统已能够检测出患者血中 ng/ml 水平的肌钙蛋白。但临床实践表明，只有在胸痛发生的 3–6 小时后才能够对肌钙蛋白水平进行可靠检测 。这使得肌钙蛋白成为 AMI 检测的“晚期”标志物。相比之下，现代高灵敏度检测试剂的检测限可突破 ng/ml而达到 pg/ml 级，这样在最初的 1–3 小时内即可发现潜在的 AMI 患者 。这种高灵敏度的肌钙蛋白检测系统使得肌钙蛋白成为了 AMI 的早期标志物。新一代高敏检测系统的敏感度比 1987 年 Cummings 首次描述的实验方法的灵敏度大约高出 1000 倍（10 pg/ml 对 10 ng/ml）。灵敏度的大幅提升有助于发现可能导致心肌组织坏死或凋亡的轻度心脏事件。



# Apple教授建议的评估高敏心肌肌钙蛋白检测性能的方案

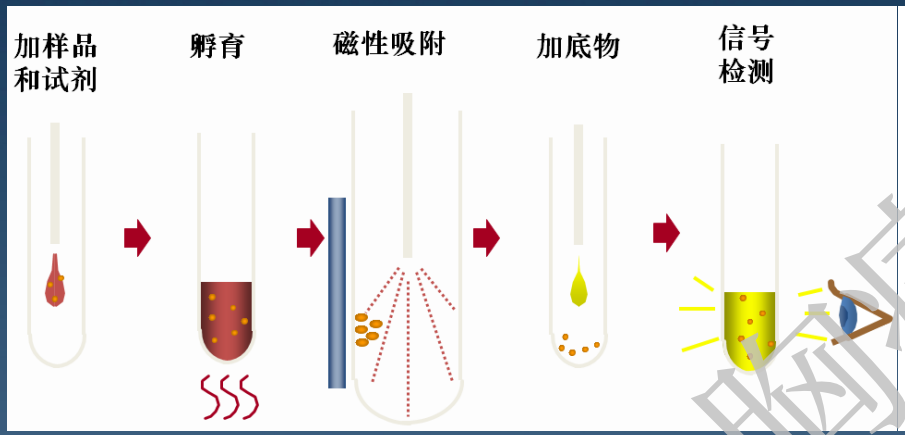
| 第99百分位值处检测不精密度(*CV*,%) | 接受程度 |
|---|---|
| ≤10 | 指南可接受 |
| >10～20 | 临床可接受 |
| >20 | 不可接受 |
| **低于第99百分位值检出率(%)** | **检测方法** |
| ≥95 | 水平4（第3代敏感方法） |
| 75～<95 | 水平3（第2代敏感方法） |
| 50～<75 | 水平2(第1代敏感方法) |
| <50 | 水平1(常规方法) |

hs-cTn应该能够在50%以上的表面健康人群中检测cTn，参考范围上限第99百分位值得检测不精密度应≤10%。

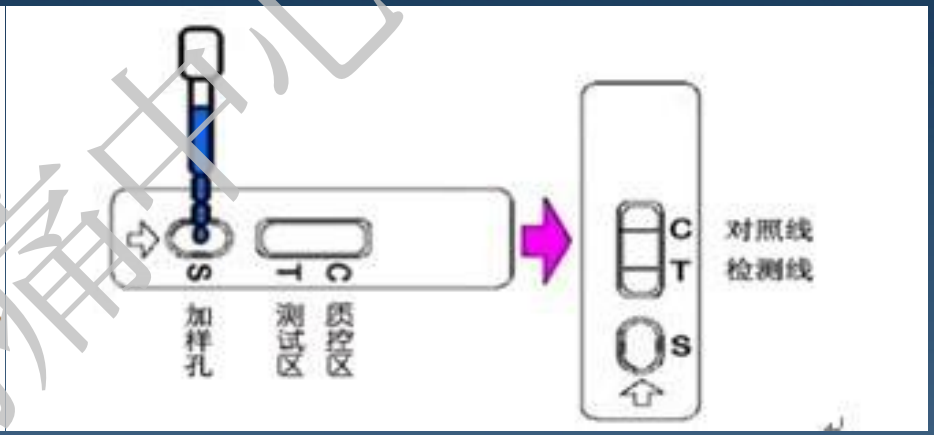
中华内科杂志2015年10月第54卷第10期

# 化学发光法比POCT能更好地检测hs-cTnI

化学发光法检测原理（单位：pg）




免疫层析法检测原理（单位：ng）




| | 液-液反应 | 清洗过程 | 低值敏感性高 | 准确性 | 灵敏度 |
|---|---|---|---|---|---|
| 化学发光法 | √ | √ | √ | √ | $10^{-18}$ |
| 免疫层析法 | × | × | × | — | $10^{-15}$ |

## 关于床旁检测肌钙蛋白（免疫层析法POCT）：

对NSTEMI的诊断，如果以中心实验室TnI＞0.2ng/ml作为诊断标准，则该床旁检测：

敏感性：68.18%

特异性：97.06%

阳性预测值：93.75%

阴性预测值：82.5%

符合率：85.71%

漏诊率：31.82%

误诊率：2.94%

北大人民心内科许俊堂教授演讲资料

# 超敏肌钙蛋白（hs-cTnI）



北京大学人民医院
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# hs-cTnI

## 1、为何使用hs-cTnI

**传统的cTn检测方法**，由于检测方法灵敏度相对不高，难以测到血循环中低水平的cTn，在缺血症状或心电图改变不典型时，有可能导致延迟诊断甚至误诊，不利于对患者的早期诊断、风险评估和预后判断。

高敏心肌肌钙蛋白在急性冠状动脉综合征中的应用中国专家共识.2012

**hs-cTn**有助于探查既往易被漏诊的微小心肌损伤、更早期诊断AMI、更合理筛查心血管事件高危患者，优化临床治疗决策与预后评估。

高敏感方法检测心肌肌钙蛋白临床应用中国专家共识（2014）

- 传统检测cTn方法的精密度无法达到在参考范围上限第99百分位值时**CV≤10%**的要求，临床实践迫切要求能够有灵敏度和精密度更高的检测方法。近年来，新的高敏感方法检测cTn的技术在临床实践中日渐增多。当前国内外尚无十分明确的**hs-cTn定义，主要根据最低检出限和测定的不精密度两方面在低cTn浓度范围的分析性能判定**（符合下列条件之一的cTn检测方法称为hs-cTn方法）：

- 高敏感方法能够检测到目前传统方法不能发现的**cTn(如低至10 ng／L或10ng/L以下)**水平；
- 符合指南要求的检测系统或试剂：检测CV≤10%的最小检测值接近第99百分位值的cTn；
- 把能在部分或全部表面健康人群中检测到cTn同时，**第99百分位值CV≤10%。**

- **胶体金方法无法实现hs-cTn（ng/L水平）的要求（只能进行普通的cTn检测），化学发光技术可以解决这个问题**

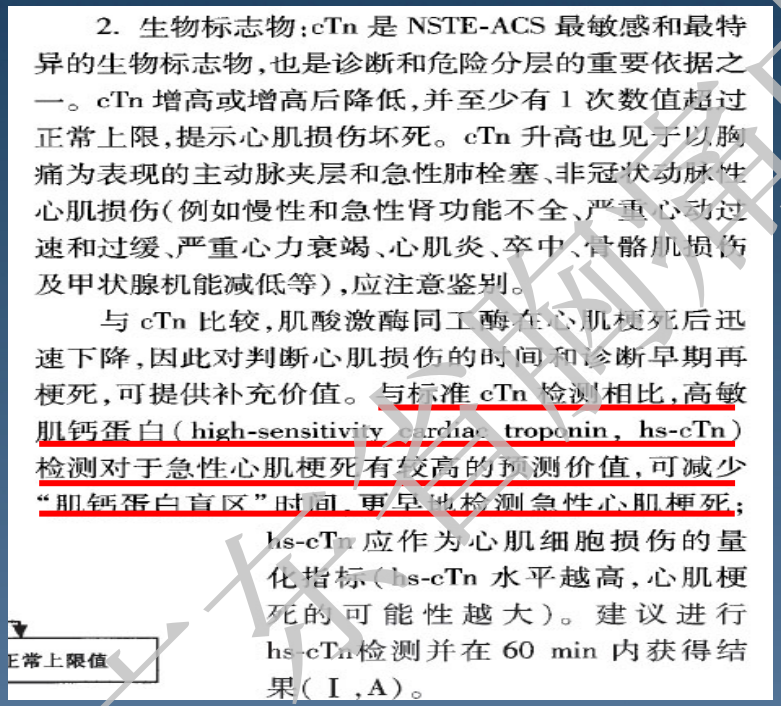
# 2、hs-cTnI更早检测心肌梗死

中华心血管病杂志 2017 年 5 月第 45 卷第 5 期　Chin J Cardiol, May 2017, Vol. 45 No. 5　· 359 ·

·指南与共识·

非 ST 段抬高型急性冠状动脉综合征诊断和治疗指南（2016）

中华医学会心血管病学分会　中华心血管病杂志编辑委员会



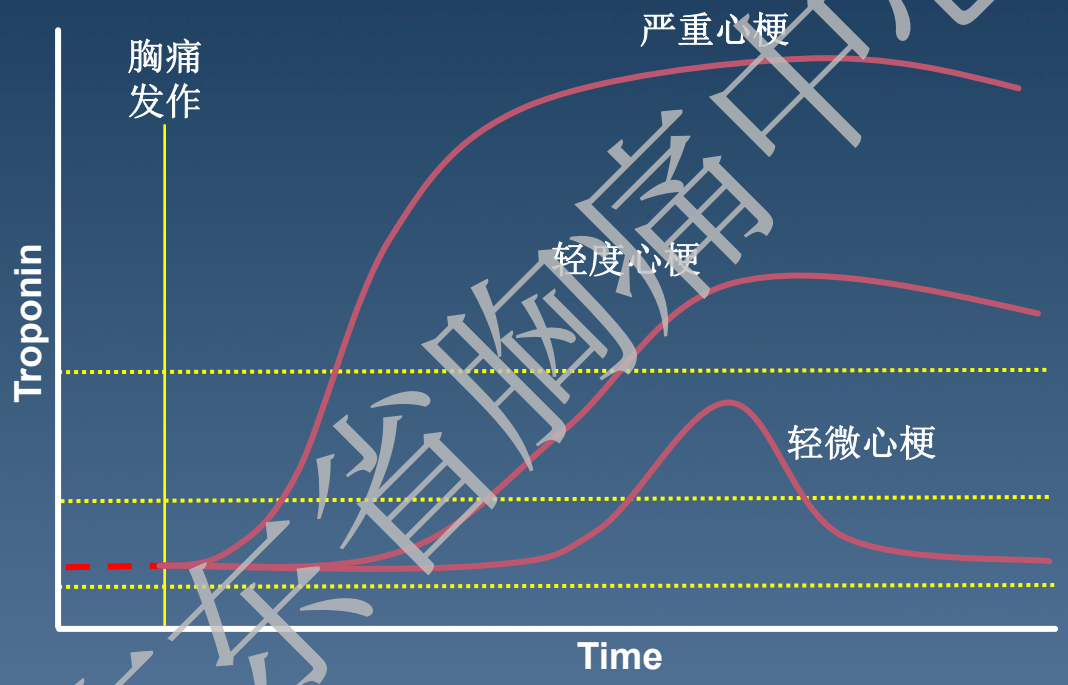
2. 生物标志物：cTn 是 NSTE-ACS 最敏感和最特异的生物标志物，也是诊断和危险分层的重要依据之一。cTn 增高或增高后降低，并至少有 1 次数值超过正常上限，提示心肌损伤坏死。cTn 升高也见于以胸痛为表现的主动脉夹层和急性肺栓塞、非冠状动脉性心肌损伤（例如慢性和急性肾功能不全、严重心动过速和过缓、严重心力衰竭、心肌炎、卒中、骨骼肌损伤及甲状腺机能减低等），应注意鉴别。

与 cTn 比较，肌酸激酶同工酶在心肌梗死后迅速下降，因此对判断心肌损伤的时间和诊断早期再梗死，可提供补充价值。与标准 cTn 检测相比，高敏肌钙蛋白（high-sensitivity cardiac troponin，hs-cTn）检测对于急性心肌梗死有较高的预测价值，可减少“肌钙蛋白盲区”时间，更早地检测急性心肌梗死；hs-cTn 应作为心肌细胞损伤的量化指标（hs-cTn 水平越高，心肌梗死的可能性越大）。建议进行 hs-cTn检测并在 60 min 内获得结果（Ⅰ，A）。

正常上限值

**hs-cTnI比cTnI更早检测心肌梗死**

# 3、hs-cTnI具有更低的检测限（参考范围上限值，URL），在URL的CV≤10%。即使轻微心梗也能早期发现




世界卫生组织
AMI 诊断值: 100 ng/L

99t百分位
MI 参考值: 14 ng/L

最低检测阈值: 3ng/L

# 4、POCT法敏感性欠佳，超敏肌钙应用化学发光法检测

中华内科杂志 2015 年 10 月第 54 卷第 10 期 Chin J Intern Med, October 2015, Vol. 54, No. 10



· 标准与讨论 ·

## 高敏感方法检测心肌肌钙蛋白临床应用中国专家共识(2014)

中华医学会心血管病学分会 中华医学会检验医学分会

7. 即时检验方式检测 cTn：随着检测技术的发展和医学科学的进步，操作简单、可快速得到检测结果的即时检验(POCT)逐步受到欢迎。采用 POCT 的方式检测 cTn 有助于缩短检测周期。选用 POCT 方式检测 cTn 的方法应该是定量的[22]。与医院检验科室采用的大中型免疫分析仪相比，POCT 方式检测 cTn 的敏感性存在一定差异。必须指出，由于 POCT 对 cTn 的检测敏感性不足[14]，当部分 POCT 检测为“阴性”时，很难确定其是否为真阴性，临床应用时应特别注意。应尽可能选择分析敏感性高的检测 cTn 的 POCT 仪器；必要时对 POCT 检测阴性的结果应采用更敏感的方法确认[23](例如可采用大中型免疫分析仪检测以明确检测结果)。生产厂商应努力提高 POCT 方式检测 cTn 的分析敏感性。

**建议 8 POCT 检测 cTn 的分析敏感性可能欠佳，临床对检测的“阴性”结果应特别注意。**

专家共识建议：POCT检测cTn的分析敏感性可能欠佳，临床对检测的“阴性”结果应特别注意

# 心型脂肪酸结合蛋白（H-FABP）



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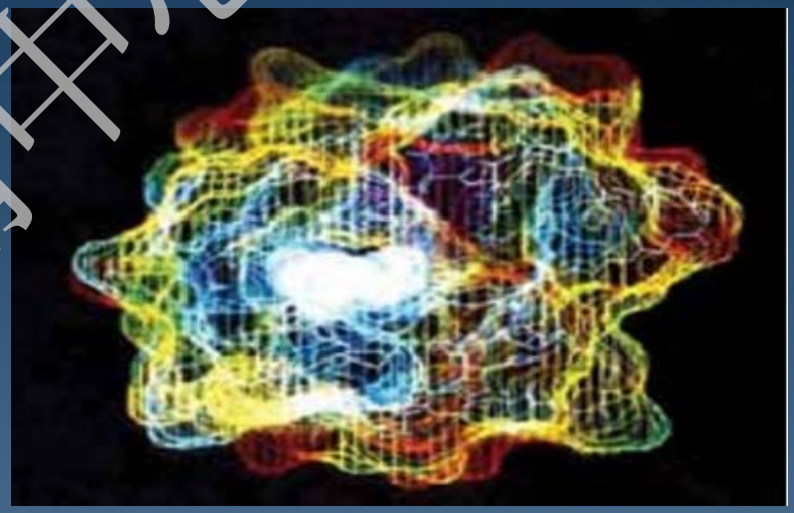
# H-FABP的来源

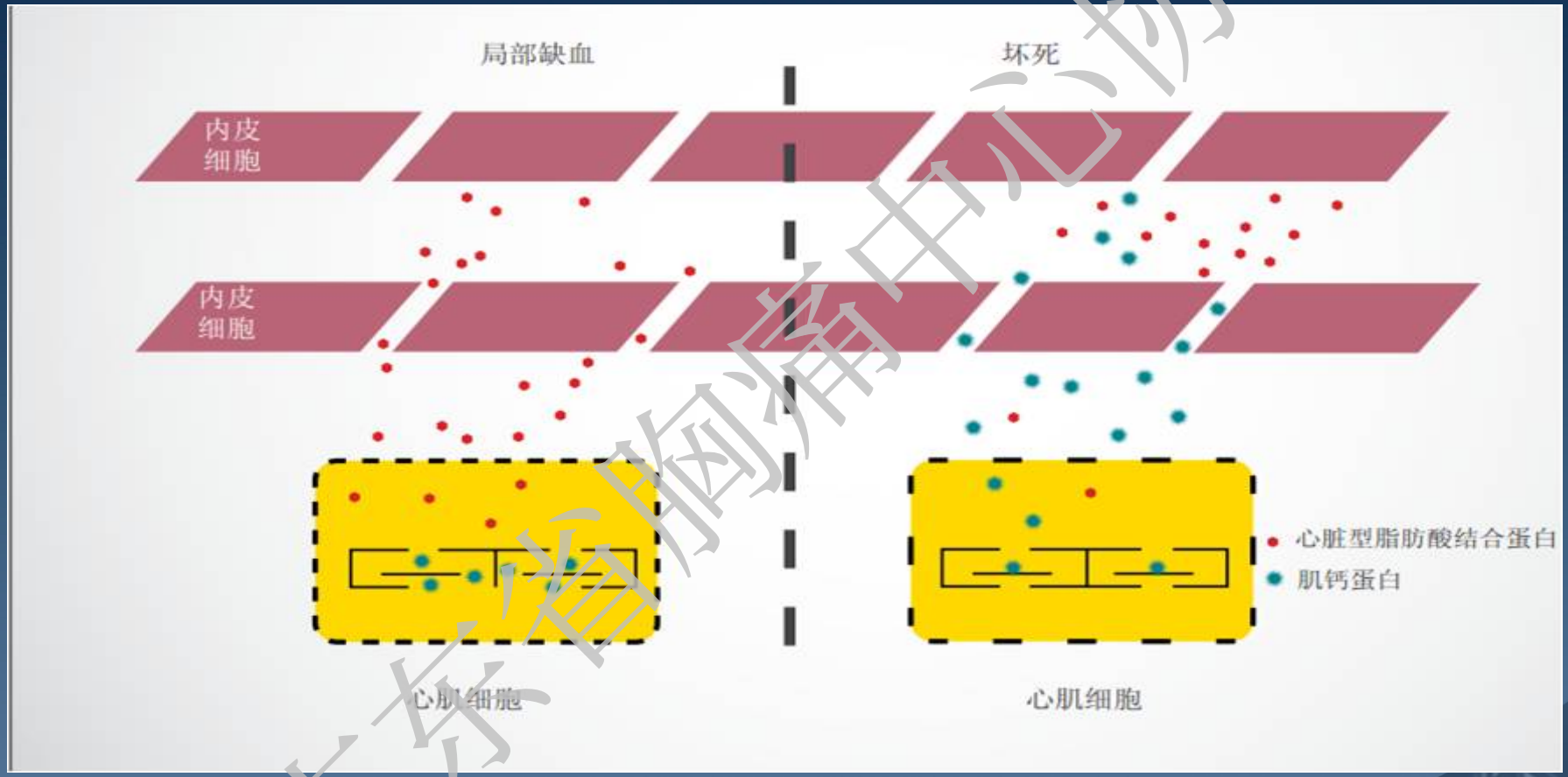
脂肪酸结合蛋白( Heart-Type Fatty Acid-Binding Protein——FABP) 是一组多源性的小分子细胞内蛋白质，分子量14 ～ 15 kDa



目前已发现的FABP有9种类型，其中心脏型FABP **(H-FABP)**较特异地存在于心肌组织中

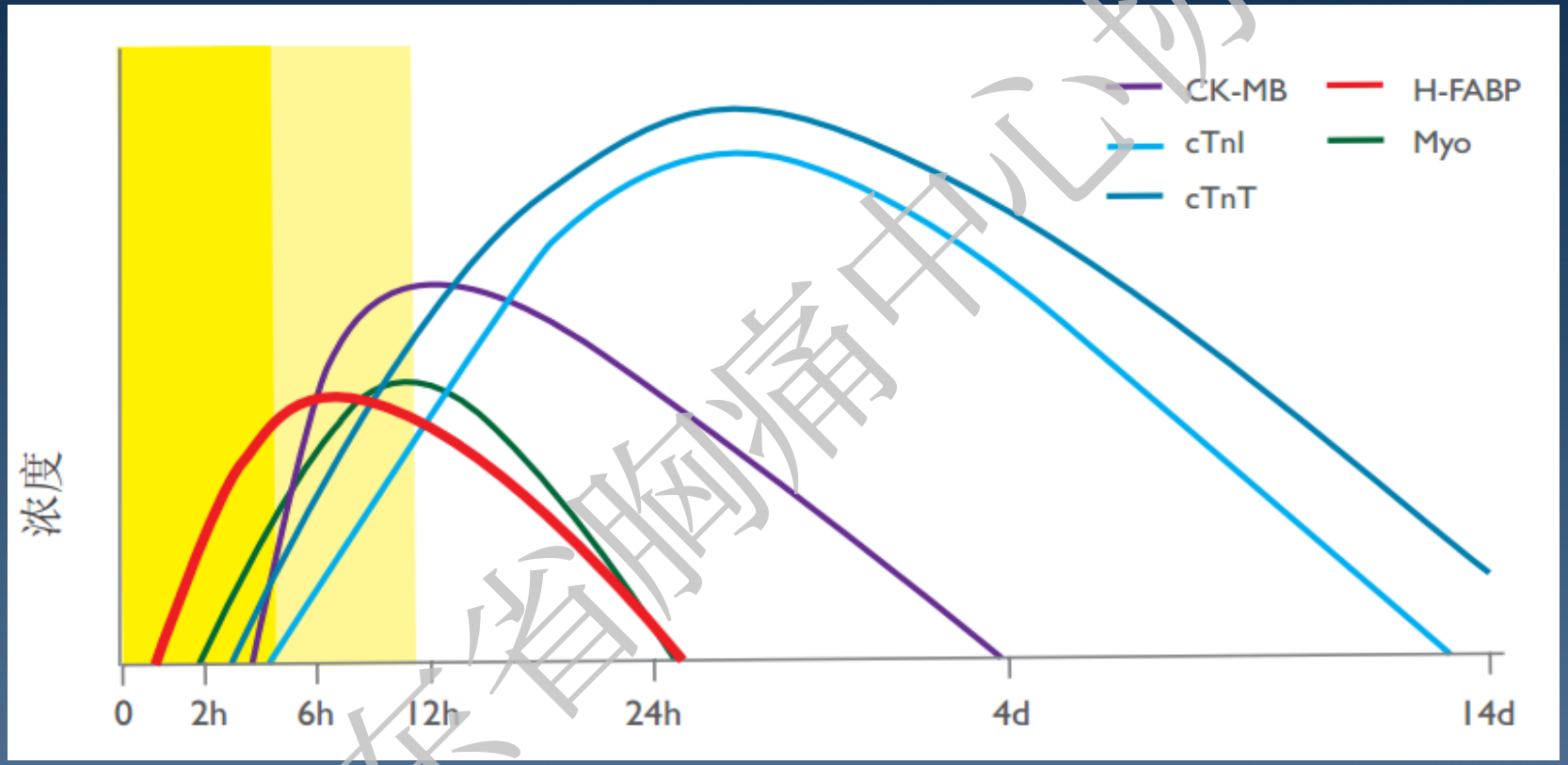
H-FABP具有高度心脏特异性——大约是肌红蛋白特异性的15-20 倍

# H-FABP的释放




H-FABP在心肌缺血早期阶段就先于cTn释放

# H-FABP的代谢




各种心肌标志物代谢时间示意图

**H-FABP最早在缺血症状发作30分钟左右可检测到**

# H-FABP专家共识

· 940 · 中华急诊医学杂志 2015 年 9 月第 24 卷第 9 期 Chin J Emerg Med, September 2015, Vol. 24, No. 9

· 专家共识 ·

## 急性非创伤性胸痛生物标志物联合检测专家共识

急性非创伤性胸痛生物标志物联合检测专家共识组

### 2.4 心型脂肪酸结合蛋白（H-FABP）

H-FABP 早期释放及快速排出的代谢动力学特点与 MYO 类似，但其心肌特异性明显高于 MYO。H-FABP 与 cTn、CK-MB 联合检测，在时间窗上合理互补将是一种临床诊治缺血性心脏病的理想选择。H-FABP 释放量与心肌损伤范围成正比，疑似 ACS 患者，低 H-FABP 浓度预示低风险，而高血 H-FABP 浓度预示患者未来发生心血管事件的风险明显增加。

H-FABP与cTn联合检测，是诊治缺血性心脏病的理想选择

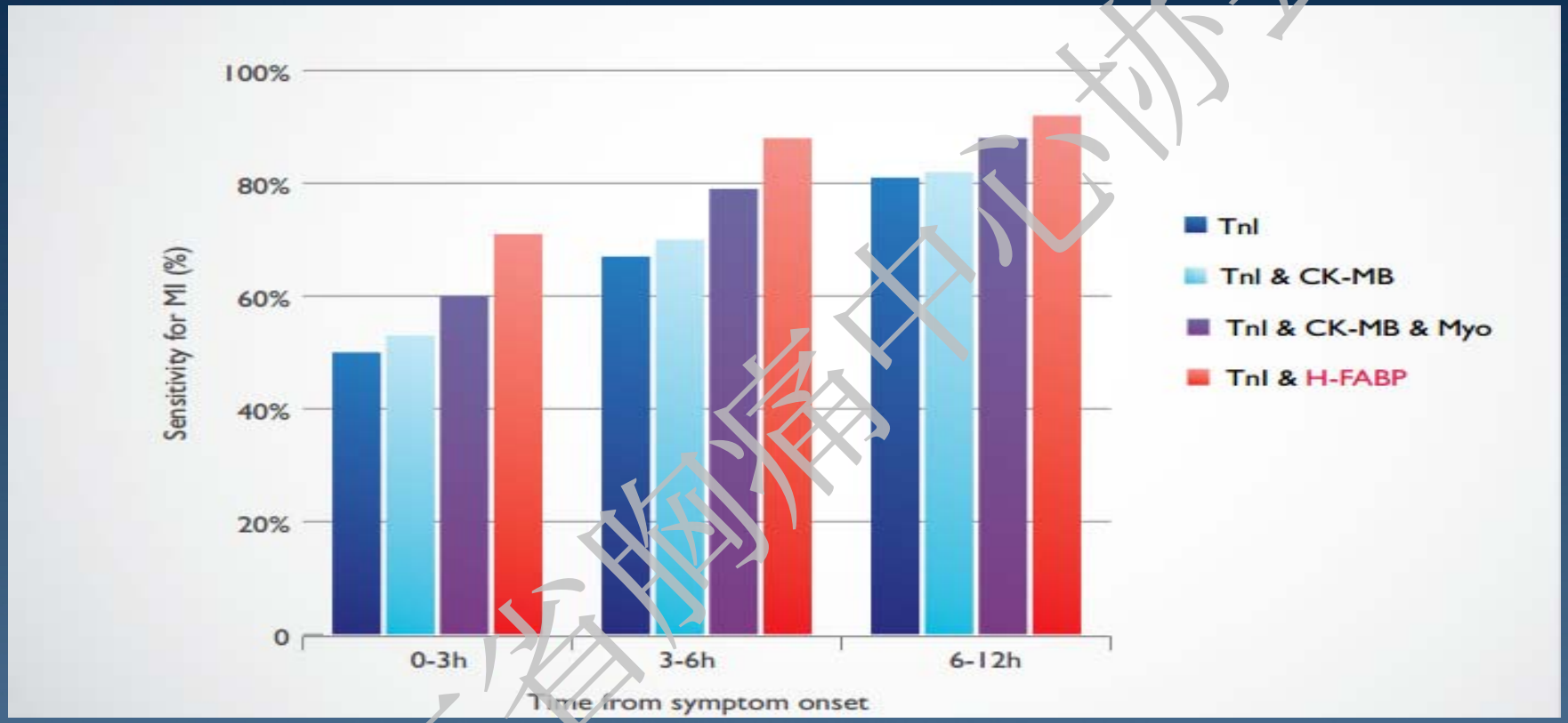
# H-FABP的临床意义

1、早期诊断急性冠状动脉综合征

2、心肌再梗死的最佳监测因子

3、急性冠状动脉综合征的危险分层

# 早期诊断ACS （1+1>3）

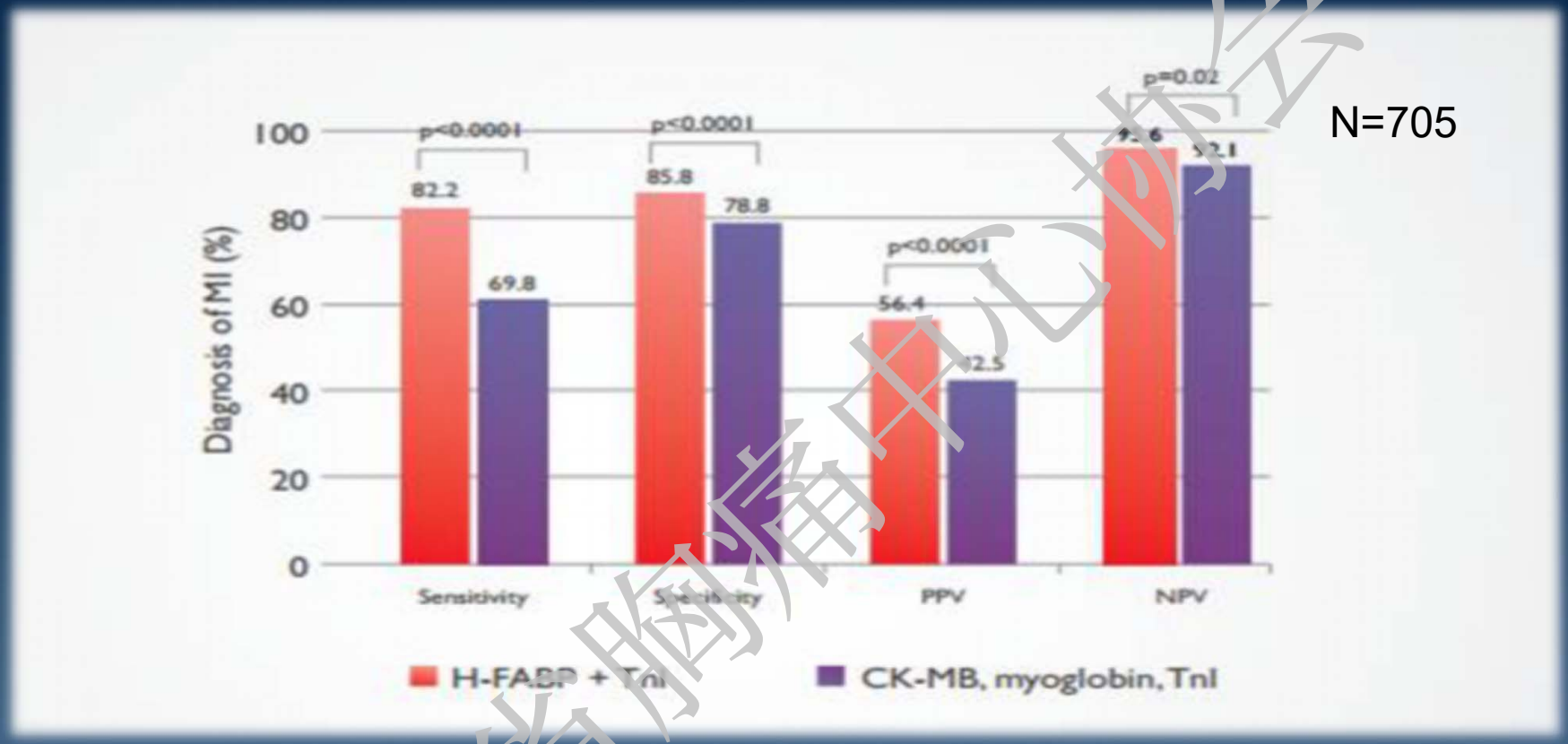



与单用cTnI或者传统心梗三项相比，H-FABP联合cTn 1+1的检测方法，可为＜12h的MI患者提供更好的诊断灵敏度。

H-FABP联合cTn 1+1的检测方法，相对于心肌三项的联合检测，仍具有优势。



Diagnostic accuracy of heart-type fatty acid–binding protein for the early diagnosis of acute myocardial infarction. **Am J Emerg Med,**2012,30(**2**):267-74.

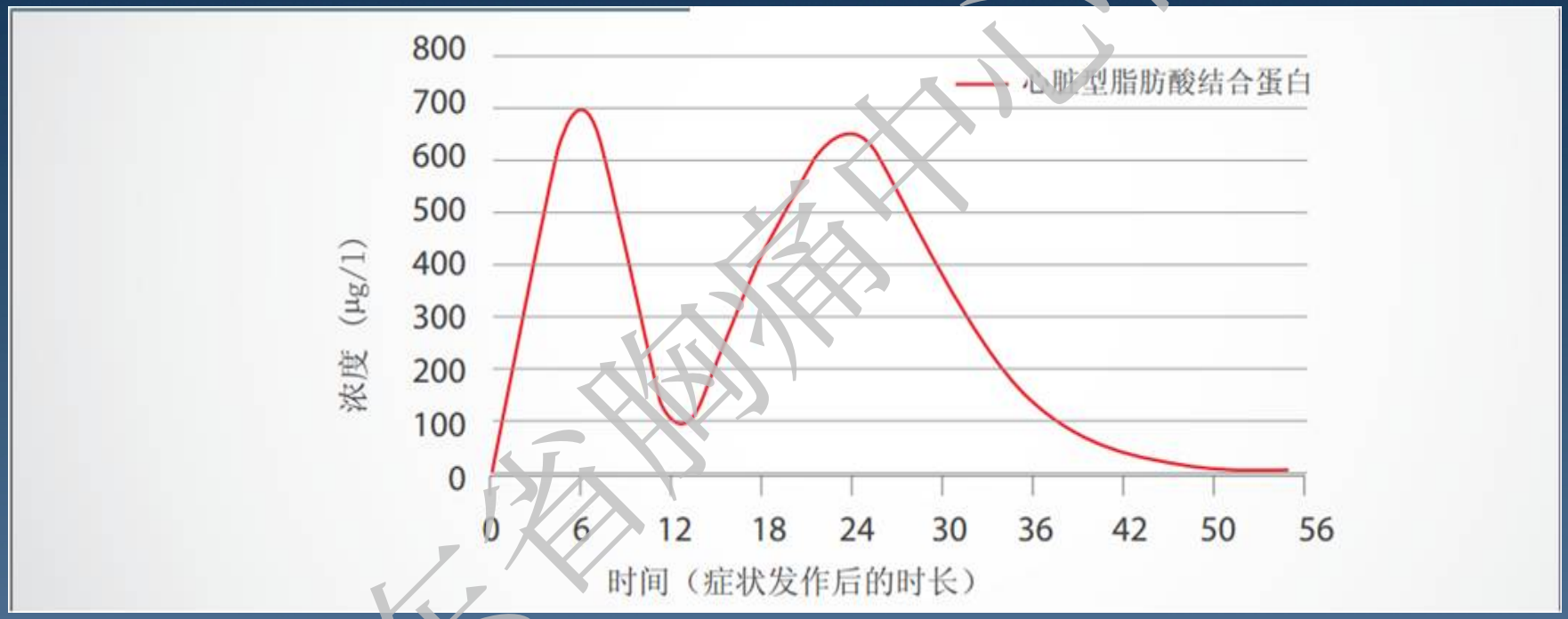



即使在患者入院后（胸痛发作 <24 小时）采血检测，H-FABP联合cTnI 1+1的检测方法在检测灵敏度、特异性、 PPV、NPV方面的Diagnostic Value仍优于传统心梗三项实现1+1>3的效果。



Body et al .Novel biomarkers in early diagnosis of acute myocardial infarction compared with cardiac troponinT.**Resuscitation**,aug,2011;82(8):1041-6.

# 心肌再梗死的最佳监测因子




H-FABP 半衰期短、特异性高，是监测再梗死的最佳标志物

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Biomarkers

# Heart-Type Fatty Acid-Binding Protein Predicts Long-Term Mortality After Acute Coronary Syndrome and Identifies High-Risk Patients Across the Range of Troponin Values

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**Objectives** Our aim was to determine if a high-performance assay for heart-type fatty acid-binding protein (H-FABP) has a role in predicting all-cause mortality after acute coronary syndrome (ACS).

**Background** Heart-type fatty acid-binding protein is released into the circulation following myocardial ischemia and necrosis and therefore may be of value to physicians when caring for patients admitted to hospital with a clinical diagnosis of ACS.

**Methods** This was a prospective observational study with a follow-up of 12 months. The H-FABP was measured 12 to 24 h after onset of symptoms in 1,548 patients admitted to hospital with ACS. The main outcome measure was all-cause mortality 1 year after index hospital admission. Multivariable analyses were conducted using the well validated GRACE (Global Registry of Acute Coronary Events) variables together with troponin I and highly sensitive C-reactive protein (hs-CRP).

**Results** After 12 months of follow-up, 296 patients had died. Multivariable analysis demonstrated that H-FABP quartiles were strongly predictive of outcome: Q1 hazard ratio (HR) 1.0; Q2 HR 2.32 (95% confidence interval [CI] 1.25 to 4.30; $p = 0.007$); Q3 HR 3.17 (1.75% CI 1.73 to 5.82; $p < 0.001$); Q4 HR 4.88 (95% CI 2.67 to 8.93; $p < 0.001$). The crude all-cause 1-year mortality for unstable angina patients with H-FABP <5.8 μg/l was 2.1% compared with 22.9% for patients above this cutoff. The adjusted all-cause mortality HR in this group was 11.35 (95% CI 2.00 to 64.34; $p = 0.006$).

**Conclusions** Heart-type fatty acid-binding protein predicts long-term mortality after ACS and identifies high-risk patients in a manner that is additive to the GRACE clinical risk factors, troponin, and hs-CRP, possibly as a result of identifying the occurrence of myocardial ischemia with or without necrosis. (J Am Coll Cardiol 2007;50:2061–7)


Heart-type fatty acid-binding protein (H-FABP) is a low-molecular-weight protein involved in the intracellular uptake and buffering of free fatty acids in the myocardium (1). It was first noted to be a marker of myocardial infarction (MI) in 1988 (2). Because it is rapidly released from the cytosol into the circulation after myocardial ischemia and necrosis (3), H-FABP has been shown to be a sensitive early marker of MI (4,5). Despite this fact, initial studies performed using nonspecific polyclonal antibody assays were disappointing. Consequently, there has been relatively little attention given to H-FABP as an early marker of myocardial necrosis/ischemia. However, O'Donoghue et al. (6) have recently reported on the prognostic value of H-FABP in a subset

See page 2068

From the *Coronary Artery Disease Clinical Research Network Group, Leeds Institute for Genetic, Health & Therapeutics, and †Clinical Trials Research Unit, University of Leeds, Leeds, United Kingdom; and the ‡Department of Clinical Biochemistry, General Infirmary at Leeds, Leeds, United Kingdom. Prof. Hall and Dr. Barth have received support in the form of free reagents from Beckman Coulter and Dainippon Pharmaceutical and research grants from AstraZeneca and Sanofi-Aventis in support of the EMMACE-2 study. Rajiv Das and Niamh Kilcullen held British Heart Foundation Junior Research Fellowships. Karthik Viswanathan is supported by grants from Pfizer and Medtronic. The structure of the EMMACE-2 Study Group is provided as an Online Appendix.

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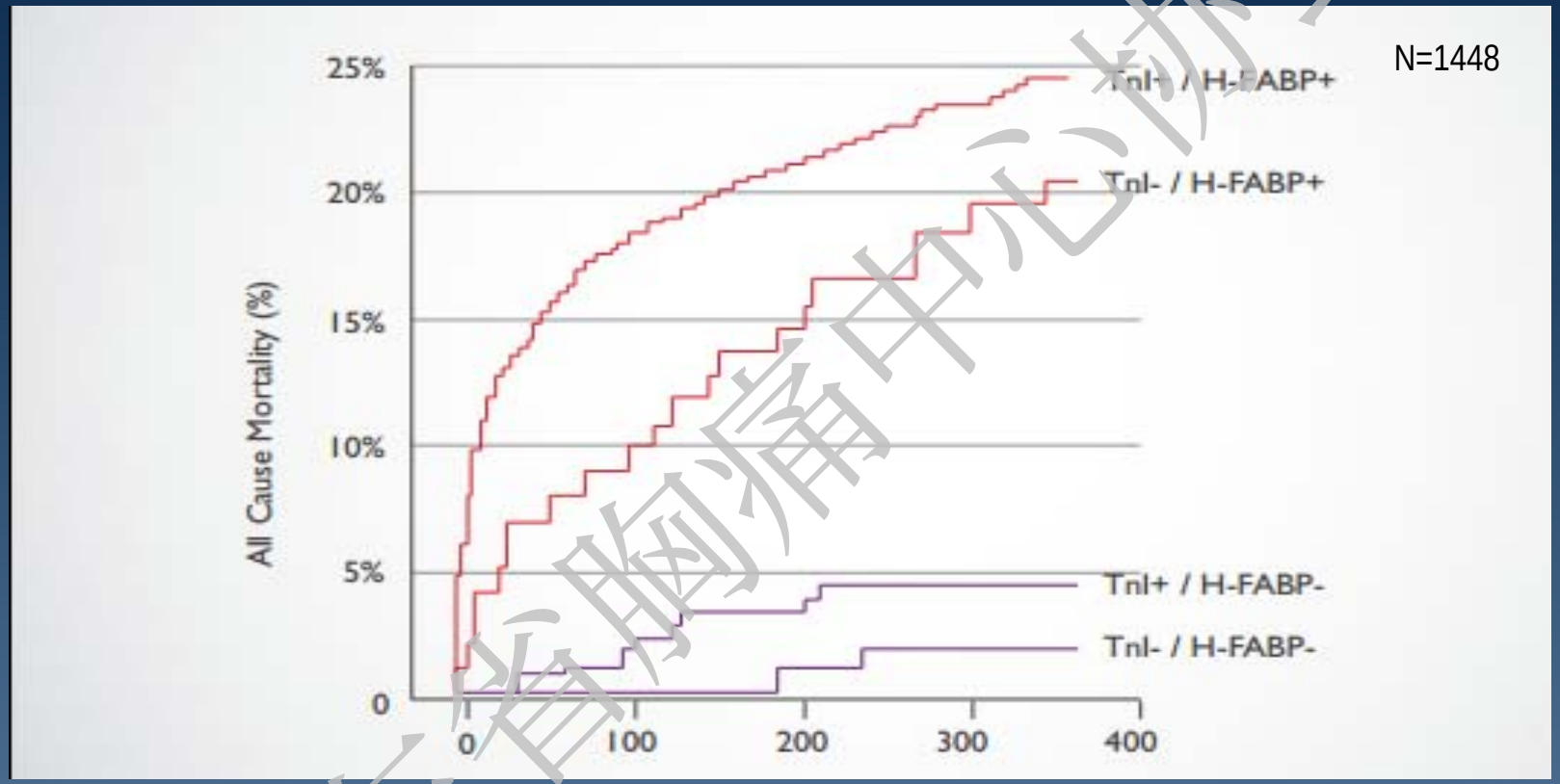


相对于cTn，H-FABP能更有效地鉴别出高危患者
H-FABP联合cTn 1+1的检测结果为阴性，则表示患者6个月内的死亡概率为0

H-FABP predicts long-term mortality after acute coronary syndrome and identifies high-risk patients across the range of troponin values. **J. Am. Coll. Cardiol**. 2007;50(21)

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Biomarkers

# Heart-Type Fatty Acid-Binding Protein Predicts Long-Term Mortality and Re-Infarction in Consecutive Patients With Suspected Acute Coronary Syndrome Who Are Troponin-Negative

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**Objectives** The purpose of this study was to establish the prognostic value of measuring heart fatty acid-binding protein (H-FABP) in patients with suspected acute coronary syndrome (ACS) (in particular, low- to intermediate-risk patients), in addition to troponin measured with the latest third-generation troponin assay.

**Background** We have previously shown that H-FABP is a useful prognostic marker in patients with proven ACS.

**Methods** Patients (n = 1,080) consecutively admitted to the hospital with suspected ACS were recruited over 46 weeks. Siemens Advia Ultra-TnI (Siemens Healthcare Diagnostics, Newbury, United Kingdom) and Randox Evidence H-FABP (Randox Laboratories, Ltd., Co. Antrim, United Kingdom) were analyzed on samples collected 12 to 24 h from symptom onset. After exclusion of patients with ST-segment elevation and new left bundle branch block, 955 patients were included in the analysis.

**Results** The primary outcome measure of death or readmission with myocardial infarction after a minimum follow-up period of 12 months (median 18 months) occurred in 96 of 955 patients (10.1%). The H-FABP concentration was an independent predictor of death or myocardial infarction, after multivariate adjustment. Patients with H-FABP concentrations ≥6.48 μg/l had significantly increased risk of adverse events (adjusted hazard ratio: 2.62, 95% confidence interval: 1.30 to 5.28, p = 0.007). Among troponin-negative patients (which constituted 79.2% of the cohort), the aforementioned cutoff of 6.48 μg/l identified patients at very high risk for adverse outcomes independent of patient age and serum creatinine.

**Conclusions** We have demonstrated that the prognostic value of elevated H-FABP is additive to troponin in low- and intermediate-risk patients with suspected ACS. Other studies suggest that our observations reflect the value of H-FABP as a marker of myocardial ischemia, even in the absence of frank necrosis. (J Am Coll Cardiol 2010; 55:2590–5) © 2010 by the American College of Cardiology Foundation

Heart-type fatty acid-binding protein (H-FABP) is a low-molecular-weight cytoplasmic protein that is involved in the intracellular uptake and buffering of free fatty acids in the myocardium (1). We have recently demonstrated that H-FABP predicts long-term mortality in a study of 1,448 patients with acute coronary syndrome (ACS) and that this prediction was independent of the GRACE (Global Registry of Acute Coronary Events) clinical risk factors, troponin and high-sensitivity C-reactive protein (2). In particular, H-FABP was able to identify those troponin-negative patients with unstable angina who were at high risk of subsequent death. This observation has been independently supported by O'Donoghue et al. (3) in their study of 2,287 ACS patients recruited in the Thrombolysis In Myocardial Infarction-16 trial. However, both these studies were performed on selected patients with independently confirmed ACS. Therefore, they offer predictive information on mortality for patients with ACS but cannot be used to provide diagnostic

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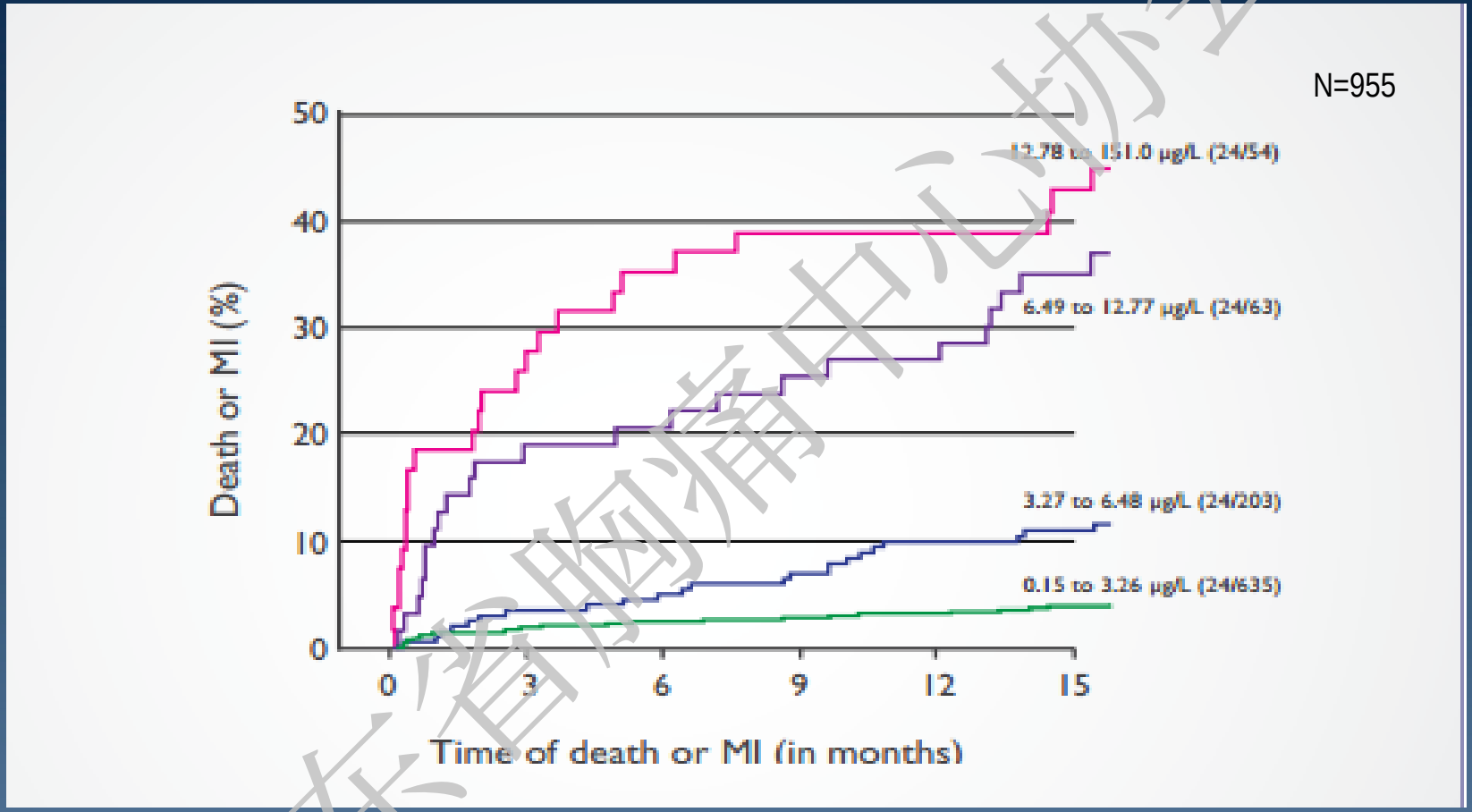


心脏型脂肪酸结合蛋白浓度＞ **12.78μg/L** 的**MI**患者具有极大的死亡风险

H-FABP Predicts Long-Term Mortality and Re-Infarction in Consecutive Patients With Suspected ACS Who Are Troponin-Negative **J. Am. Coll. Cardiol. 2010**;55(23): 2590-8

# 7分钟小型全自动化学发光仪



北京大学人民医院
Peking University People's Hospital

# 1、NRM S7 突破胸痛中心认证标准要求，助力胸痛中心建设

仪器 小：可以在门急诊及临床科室使用，可急诊可批量；

结果 快：7分钟快速出诊断结果，全自动；

结果 准：直接化学发光法，全定值，抗干扰能力强；

项目 全：检测全程心血管事件标记物，检测超敏肌钙；

采样 方便：支持全血、血浆快速检测；

重复性 好：批内CV≤5%，批间CV≤8%；

北京大学人民医院
Peking University People's Hospital

# 2、顺应胸痛中心的建设快速发展需求

- 全球第一家“胸痛中心”于**1981**年在美国建立，至今美国“胸痛中心”已经发展到**5000**余家
- 目前中国**CPC**约**500**多家，**2018**年需要建设到**1000**家以上

# 3、推动胸痛中心的认证标准

中国介入心脏病学杂志 2016 年 3 月第 24 卷第 3 期 Chin J Intervent Cardiol, March 2016, Vol 24, No. 3 ·121·

·规范与标准·

中国胸痛中心认证标准(2015 年 11 月修订)

中国胸痛中心认证工作委员会

集心电图；无持续或复发性症状且临床情况稳定的患者应在不超过4 h 内复查心电图。b. 确定心肌生化标志物诊断 NSTEMI 的标准界值，生化标志物中必须包含肌钙蛋白，有条件时应开展超敏肌钙蛋白检测，以满足快速评估和早期诊断的需要，应确保能在抽血后 20 min 获得肌钙蛋白检测结果。c. 若首次肌钙蛋白为阴性，则应在入院后 6 h 内复查，若采用高敏肌钙蛋白，则应根据当前指南确定复查时间。

胸痛中心的认证标准（20 min）出结果

# 7分钟出结果，突破胸痛中心认证标准（20 min），助力胸痛中心建设

适应科室：

1. 可同时检测Hs-cTn,H-FABP,ck-mb,MYO,D-D,NT-ProBNP，满足ACS快速辅助诊断的需求
2. 胸痛中心、心内科病房和ICU、门、急诊检验科
3. 医联体互认，替代荧光POCT
4. 开展多中心、大样本的课题研究，推动专家共识和指南的建设（hs-cTnI和H-FABP）

北京大学人民医院
Peking University People's Hospital

# *Thank you for Your Attention!*



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